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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/500,511 | 06/30/2004 | Stephen Francis Badylak | 3220-72178 | 6418 |

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| EXAMINER | |
|---|---|
| CHEN, SHIN LIN | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 11/02/2009 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

indocket@btlaw.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/500,511 | BADYLAK ET AL. | |
| | Examiner | Art Unit | |
| | Shin-Lin Chen | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *1-10 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-15 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9-24-09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9-24-09 has been entered.

Applicants' amendment filed 9-24-9 has been entered. Claims 11 and 19 have been amended. Claims 20 and 21 have been canceled. Claims 1-19 are pending. Claims 11-15 and 17-19 are under consideration.

***Claim Rejections - 35 USC § 103***

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 11-15 and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Badylak, Stephen, 2002 (US Patent No. 6,379,710 B1, IDS-AG) or Badylak, Stephen, 1998 (WO 98/25637) each in view of Badylak et al., 2007 (US Patent No. 7,175,841 B2).

Claims 11-15 are directed to a purified liver basement membrane graft composition comprising basement membrane of warm-blooded vertebrate liver tissue, wherein the DNA content of the liver basement membrane is at an average of 0.303 and a standard deviation of 0.263 ug of DNA/mg of dry weight of basement membrane and wherein the graft composition is remodelable upon implantation. Claims 12-14 specify the liver basement membrane is fluidized, in a gel form or in powder form. Claim 15 specifies the liver basement membrane is substantially free of cells of the warm-blooded vertebrate. Claims 17 and 18 are directed to a liver tissue derived composition for supporting cell growth and the composition comprises the liver basement membrane of claim 11 or comprises culture-ware coated with a matrix comprising the liver basement membrane of claim 11, wherein the liver basement membrane is devoid of source liver tissue endogenous cells. Claim 19 is directed to a collagenous tissue graft structure comprising decellularized basement membrane wherein the DNA content of the liver basement membrane is at an average of 0.303 and a standard deviation of 0.263 ug of DNA/mg of dry weight of basement membrane and wherein the graft composition is remodelable upon implantation.

Badylak (2002) teaches a tissue graft composition comprising liver basement membrane prepared by removing the cellular components from liver tissue by treating the liver tissue with a solution comprising an enzyme, such as trypsin or pepsin, and a calcium chelating agent or chaotropic agent such as a mild detergent Triton 100, or with a solution comprising only the

chelating agent or chaotropic agent (e.g. abstract, column 3, lines 1-15). The liver tissue slice can be suspended in an agitated solution containing protease, optionally containing a chaotropic agent or a calcium chealating agent in an amount effective to optimize release and separation of cells from the basement membrane without substantial degradation of the membrane matrix (e.g. column 3, lines 16-24). Badylak further teaches that the liver basement membrane can be fluidized or in powder form (e.g. column 3, lines 39-60, column 11, 12), cell growth substrate are formed from fluidized forms of liver basement membrane and the fluidized tissue can be gelled to form solid or semi-solid matrix (e.g. column 8, lines 12-18), and the cell growth substrate can be combined with nutrients, such as minerals, amino acids, sugars, peptides, proteins, glycoproteins that facilitate cellular proliferation and growth factors (e.g. column 8, lines 26-32). Badylak also teaches that "fluidized forms of liver basement membrane can be used to coat culture-ware with a matrix comprising liver basement membrane devoid of source liver tissue endogenous cells. Thus, liver basement membrane can be used as a cell growth substrate in a variety of forms, including a sheet-like configuration, as a gel matrix, as an additive for art-recognized cell/tissue culture media, or as coating for culture-ware to provide a more physiologically relevant substrate that support and enhances the proliferation of cells" (e.g. column 7, lines 48-53).

Badylak (1998) teaches a tissue graft composition comprising liver basement membrane prepared by removing the cellular components from liver tissue by treating the liver tissue with a solution comprising an enzyme, such as trypsin or pepsin, and a calcium chelating agent or chaotropic agent such as a mild detergent Triton 100, or with a solution comprising only the chelating agent or chaotropic agent (e.g. abstract, p. 3-4). The liver tissue slice can be suspended

in an agitated solution containing protease, optionally containing a chaotropic agent or a calcium chealating agent in an amount effective to optimize release and separation of cells from the basement membrane without substantial degradation of the membrane matrix (e.g. p. 4). Badylak further teaches that the liver basement membrane can be fluidized or in powder form (e.g. p. 4-5, 16), cell growth substrate are formed from fluidized forms of liver basement membrane and the fluidized tissue can be gelled to form solid or semi-solid matrix (e.g. p. 11, second paragraph), and the cell growth substrate can be combined with nutrients, such as minerals, amino acids, sugars, peptides, proteins, glycoproteins that facilitate cellular proliferation and growth factors (e.g. p. 11, third paragraph). Badylak also teaches that "fluidized forms of liver basement membrane can be used to coat culture-ware with a matrix comprising liver basement membrane devoid of source liver tissue endogenous cells. Thus, liver basement membrane can be used as a cell growth substrate in a variety of froms, including a sheet-like configuration, as a gel matrix, as an additive for art-recognized cell/tissue culture media, or as coating for culture-ware to provide a more physiologically relevant substrate that support and enhances the proliferation of cells" (e.g. p. 10, 2nd paragraph).

Badylak does not specifically teach the DNA content of the liver basement membrane is at an average of 0.303 and a standard deviation of 0.263 ug of DNA/mg of dry weight of basement membrane.

Badylak (2007) teaches an improved tissue graft construct comprising submucosa of a warm-blooded vertebrate and a preselected group of eukaryotic cells to enhance the repair of damaged or diseased tissue in vivo (e.g. abstract). Badylak determines DNA content of the cartilaginous tissue formed on an intestinal submocosa is about 0.86+_0.2 ug DNA/mg dry

weight and the intestinal submucosa has a DNA content of 2.04+_0.1 ugDNA/mg dry weight (e.g. column 21, lines 11-29). Badylak also teaches that "Porcine small intestinal submucosa is a resorbable biomaterial that upon implantation induces tissue remodeling" (e.g. column 17, lines 44-45).

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to prepare a liver basement membrane graft composition comprising basement membrane having DNA content of 0.303+_0.263 ugDNA/mg dry weight of basement membrane because Badylak (2007) discloses the DNA content of the cartilaginous tissue at about 0.86+_0.2 ug DNA/mg dry weight and the intestinal submucosa has a DNA content of 2.04+_0.1 ugDNA/mg dry weight, and intestinal submucosa is a type of tissue graft containing collagenous matrix and a cartilaginous tissue is primarily extracellular matrix containing collagen type II and large amount of proteoglycan. A basement membrane is a type of tissue graft. It would be obvious to one of ordinary skill in the art to prepare the liver basement membrane composition having the claimed DNA content since preparation of a liver basement membrane composition was known, as taught by Badylak, and determining the DNA content of a tissue graft and to have various different DNA contents in various tissue graft would be obvious to one of ordinary skill. It is noted that Badylak (2007) does teach the small intestinal submucosa can induce tissue remodeling upon implantation and it also is inherent that the tissue graft composition as taught by Badylak (2002) or Badylak (1998) is remodelable upon implantation.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to use the liver basement membrane as a cell growth substrate in a variety of forms, or as coating for culture-ware to provide a more physiologically relevant

substrate that support and enhances the proliferation of cells as taught by Badylak (2002 & 1998) or to prepare a tissue graft for repairing damaged or diseased tissue in vivo as taught by Badylak (2007) with reasonable expectation of success.

5. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Robinson et al., 1980 (European Journal of Biochemistry/FEBS, Vol. 111, No. 2, pp. 485-490) in view of Badylak et al., 2007 (US Patent No. 7,175,841 B2).

Claim 19 is directed to a collagenous tissue graft structure comprising decellularized basement membrane wherein the DNA content of the liver basement membrane is at an average of 0.303 and a standard deviation of 0.263 ug of DNA/mg of dry weight of basement membrane and wherein the graft composition is remodelable upon implantation.

Robinson teaches isolating basement membrane from rabbit kidney using detergent N-dodecyl sarcosine, the residual proteins were collagenous and the extracted membranes retained their continuity of structure and exhibited a matrix composed of fibrous and globular elements. The filtration properties of the membranes were studied in vitro and show an enhanced capacity to retain proteins (e.g. abstract).

Robinison does not specifically teach the DNA content of the liver basement membrane is at an average of 0.303 and a standard deviation of 0.263 ug of DNA/mg of dry weight of basement membrane.

Badylak (2007) teaches an improved tissue graft construct comprising submucosa of a warm-blooded vertebrate and a preselected group of eukaryotic cells to enhance the repair of damaged or diseased tissue in vivo (e.g. abstract). Badylak determines DNA content of the

cartilaginous tissue formed on an intestinal submocosa is about 0.86+_0.2 ug DNA/mg dry weight and the intestinal submucosa has a DNA content of 2.04+_0.1 ugDNA/mg dry weight (e.g. column 21, lines 11-29). Badylak also teaches that "Porcine small intestinal submucosa is a resorbable biomaterial that upon implantation induces tissue remodeling" (e.g. column 17, lines 44-45).

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to prepare a liver basement membrane graft composition comprising basement membrane having DNA content of 0.303+_0.263 ugDNA/mg dry weight of basement membrane because Badylak (2007) discloses the DNA content of the cartilaginous tissue at about 0.86+_0.2 ug DNA/mg dry weight and the intestinal submucosa has a DNA content of 2.04+_0.1 ugDNA/mg dry weight, and intestinal submucosa is a type of tissue graft containing collagenous matrix and a cartilaginous tissue is primarily extracellular matrix containing collagen type II and large amount of proteoglycan. A basement membrane is a type of tissue graft. It would be obvious to one of ordinary skill in the art to prepare the collagenous tissue graft comprising decellularized basement membrane having the claimed DNA content since preparation of a collagenous basement membrane composition was known, as taught by Robinson, and determining the DNA content of a tissue graft and to have various different DNA contents in various tissue graft would be obvious to one of ordinary skill. It is noted that Badylak (2007) does teach the small intestinal submucosa can induce tissue remodeling upon implantation.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to study filtration properties of the basement membranes in vitro as

taught by Robinson or to prepare a tissue graft for repairing damaged or diseased tissue in vivo as taught by Badylak (2007) with reasonable expectation of success.

6. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Brendel et al., 1980 (Advances in Experimental Medicine and Biology, Vol. 131, pp. 89-103) in view of Badylak et al., 2007 (US Patent No. 7,175,841 B2).

Claim 19 is directed to a collagenous tissue graft structure comprising decellularized basement membrane wherein the DNA content of the liver basement membrane is at an average of 0.303 and a standard deviation of 0.263 ug of DNA/mg of dry weight of basement membrane and wherein the graft composition is remodelable upon implantation.

Brendel teaches isolation of vascular basement membrane from several organs, such as kidney, lung, placenta and brain, via nondisruptive detergent solubilization techniques with detergent and DNase (e.g. p. 89, Table 1). The vascular basement membrane is decellularized and the remaining materials include basement membrane, interstitial collagen and a few other proteins such as fibrin, tubulin and actin (e.g. p. 91, 1st paragraph).

Brendel does not specifically teach the DNA content of the liver basement membrane is at an average of 0.303 and a standard deviation of 0.263 ug of DNA/mg of dry weight of basement membrane.

Badylak (2007) teaches an improved tissue graft construct comprising submucosa of a warm-blooded vertebrate and a preselected group of eukaryotic cells to enhance the repair of damaged or diseased tissue in vivo (e.g. abstract). Badylak determines DNA content of the cartilaginous tissue formed on an intestinal submocosa is about 0.86+_0.2 ug DNA/mg dry

weight and the intestinal submucosa has a DNA content of 2.04+_0.1 ugDNA/mg dry weight (e.g. column 21, lines 11-29). Badylak also teaches that "Porcine small intestinal submucosa is a resorbable biomaterial that upon implantation induces tissue remodeling" (e.g. column 17, lines 44-45).

It would have been prima facie obvious for one of ordinary skill in the art at the time of the invention to prepare a liver basement membrane graft composition comprising basement membrane having DNA content of 0.303+_0.263 ugDNA/mg dry weight of basement membrane because Badylak (2007) discloses the DNA content of the cartilaginous tissue at about 0.86+_0.2 ug DNA/mg dry weight and the intestinal submucosa has a DNA content of 2.04+_0.1 ugDNA/mg dry weight, and intestinal submucosa is a type of tissue graft containing collagenous matrix and a cartilaginous tissue is primarily extracellular matrix containing collagen type II and large amount of proteoglycan. A basement membrane is a type of tissue graft. It would be obvious to one of ordinary skill in the art to prepare the collagenous tissue graft comprising decellularized basement membrane having the claimed DNA content since preparation of a collagenous basement membrane composition was known, as taught by Brendel, and determining the DNA content of a tissue graft and to have various different DNA contents in various tissue graft would be obvious to one of ordinary skill. It is noted that Badylak (2007) does teach the small intestinal submucosa can induce tissue remodeling upon implantation.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to prepare a tissue graft for repairing damaged or diseased tissue in vivo as taught by Badylak (2007) with reasonable expectation of success.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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